II. REMARKS

Upon entry of the amendment, claims 1 and 70 to 75 will be pending. A marked version showing the amendments to the specification and claims is attached hereto as Exhibit A.

A. Regarding the Amendments

The Title has been amended to more clearly reflect the subject matter under examination. As such, the amendment merely addresses a formality, and does not add new matter.

The specification has been amended at page 1 to update the priority information, and in the paragraph bridging pages 44 to 45 to correct typographical errors. As such, the amendments merely address formalities, and do not add new matter.

Claims 2, 4 and 5 and, pursuant to the Restriction Requirement, claims 3 and 6 to 69 are cancelled herein without disclaimer, and without prejudice to Applicants' pursuing prosecution of subject matter encompassed within one or more of the claims in an application claiming the benefit of priority of the subject application.

Claim 1 has been amended to incorporate the language of original claims 2, 4 and 5, which previously depended from claim 1. As such, the amendment to claim 1 is supported by the claims as originally filed (see, also, page 6, lines 24-26; and page 18, lines 5-11) and, therefore, does not add new matter.

New claims 70 to 75 have been added. New claims 70 and 71 are supported, for example, at page 26, lines 26-27, and Example 2 at page 52 (see, also, original claims 21 and 22). New claims 72 to 75 are supported, for example, at page 5, lines 1-8; and page 26, lines 7-13. As such, the newly added claims do not add new matter.

B. Regarding the Title and Specification

It is stated in the Office Action that the Title is not descriptive. The Title has been amended along the lines suggested by the Examiner, and is submitted to be descriptive of the subject matter under examination. As such, it is respectfully requested that this objection be withdrawn.

The specification is objected to as not reciting the serial number of the priority application, and for various typographical errors. The specification has been amended to attend to these informalities. As such, it is respectfully requested that this objection be withdrawn.

C. Claim Objection

Claim 5 is objected to as directed to non-elected subject matter. Claim 5 has been cancelled and, therefore, it is submitted that this objection is moot.

D. Rejections under 35 U.S.C. § 112

The objection to the specification and corresponding rejection of claims 1, 2, 4 and 5 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement are respectfully traversed.

It is stated in the Office Action that the claims broadly encompass any means of modulating Aβ11-40/42 peptide production including, for example, by using an "agent", which can be an antisense molecule, an antibody, or any chemical or biological compound, to modulate proteolytic activity, enzyme activity, or gene transcription, the only requirement being that production of the Aβ11-40/42 peptide is modulated. Although it is submitted that the specification broadly enables modulating production of the Aβ11-40/42 peptide by effecting BACE1 expression or activity, the claims have been amended pursuant to the restriction requirement and species election. As such, the rejection is addressed specifically with respect to the subject matter under examination.

Claim 1 is directed to a method of inhibiting production of the Aβ11-40/42 peptide by contacting a sample or cell containing a beta-site APP-cleaving enzyme 1 (BACE1) and an

amyloid precursor protein (APP) *in vitro* with an antibody specific for BACE1, whereby the antibody inhibits BACE1 cleavage of APP, thereby inhibiting the production of Aβ11-40/42 peptide fragments. It is stated in the Office Action that the specification does not teach how to overcome obstacles, for example, specific biological actions/activities that the compounds would effect, or how an antibody would effect peptide formation However, the amended claims require the use of an anti-BACE1 antibody, which is specific for BACE1, to inhibit BACE1 cleavage of APP, thus inhibiting production of Aβ11-40/42 peptide fragments from APP.

It is submitted that one skilled in the art reasonably would have known that an antibody specific for BACE1 would be useful for inhibiting BACE1 activity because it is well known, for example, that an antibody can bind at or near the substrate binding site of an enzyme, thus inhibiting binding of the substrate by the enzyme and, therefore, the enzymatic activity. As such, the skilled artisan, viewing the subject application, would have known that an anti-BACE1 antibody can bind at or near the APP binding site of BACE1, thereby inhibiting the interaction of BACE1 with APP and, therefore, BACE1 mediated cleavage of APP to produce Aβ11-40/42 peptide fragments. Furthermore, the specification teaches the skilled artisan how to make and use anti-BACE1 antibodies (page 52, Example 2), and discloses how to identify Aβ11-40/42 peptide fragment production (page 55, Example 4; see, also, page 56, lines 1-18).

For the above reasons, it is submitted that undue experimentation would not have been required for one skilled in the art to practice the claimed invention because the subject application discloses how to make and use anti-BACE1 antibodies and how to identify the production of Aβ11-40/42 peptide fragments due to BACE1 cleavage of APP. Accordingly, it is respectfully requested that the rejection of the claims under 35 U.S.C. § 112, first paragraph, be removed.

The rejection of claims 1, 2, 4 and 5 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite is respectfully traversed.

It is stated in the Office Action that the method steps do not indicate how an anti-BACE1 antibody affects Aβ11-40/42 peptide fragment production such that the antibody can be considered a modulator. Claim 1 has been amended to more clearly indicate that an antibody

specific for BACE1 inhibits BACE1 cleavage of APP, thereby inhibiting production of Aβ11-40/42 peptide fragments. As such, it is submitted that the claims clearly define the subject matter regarded as the invention and, therefore, is respectfully requested that the rejection of the claims under 35 U.S.C. § 112, second paragraph, be removed.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice that effect respectfully is requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions related to this matter.

If any additional fees are deemed necessary (or if any overpayment has been made), the Commissioner is authorized to charge (or credit) Deposit Account No.: 50-1355.

Respectfully submitted,

Date: January 10, 2003

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EXHIBIT A

MARKED VERSION SHOWING AMENDMENTS

The specification has been amended at page 1, lines 6-8, as follows [Note: underlining between brackets was in application as filed, and is deleted by the amendment]:

This application claims priority under 35 U.S.C. §119(e)(1) from Provisional Application Serial No. [_____] 60/244,051, filed October 27, 2000, entitled "Beta-Secretase (BACE1) Knockout Mice".

The specification also has been amended at pages 44 to 45, as follows:

The positive selectable marker encodes a selectable marker which affords a means for selecting cells which have integrated targeting transgene sequences. The negative selectable marker encodes a selectable marker which affords a means for selecting cells which do not have an integrated copy of the negative selection expression cassette. Thus, by a combination positive-negative selection protocol, it is possible to select cells that have undergone homologous replacement recombination and incorporated the portion of the transgene between the homology regions (*i.e.*, the replacement region) into a chromosomal location by selecting for the presence of the positive marker and for the absence of the negative marker. Preferred selectable markers for inclusion in the targeting constructs of the invention encode and express a selectable drug resistance marker and/or a HSV thymidine kinase enzyme. Suitable drug resistance genes include, for example: gpt (xanthine-guanine phosphoribosyltransferase), which can be selected for with mycophenolic acid; neo (neomycin phosphotransferase), which can be selected for with G418 or hygromycin; and DFHR (dihydrofolate reductase), which can be selected for with methotrexate (Mulligan and Berg (1981) Proc. [Matl.] Natl. Acad. Sci. (U.S.A.) 78: 2072; [southern] Southern and Berg (1982) J. Mol. Appl. Genet. 1: 327; which are incorporated herein by reference).

Claim 1 has been amended as follows:

1. (Amended) A method for [modulating the] inhibiting production of Aβ11-40/42 peptide fragments, comprising contacting a sample or cell containing a beta-site APP-cleaving enzyme 1 (BACE1) and an amyloid precursor protein (APP) *in vitro* with [a BACE1-modulating agent such that] an antibody specific for BACE1, whereby the antibody inhibits BACE1 cleavage of APP, thereby inhibiting the production of Aβ11-40/42 peptide fragments [is modulated].